Extreme Drug Resistance (XDR) in Nosocomial Pathogens

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The implacable increase in the prevalence of antimicrobial resistance among gran negative bacilli (BGN) is of great concern. Several highly resistant gram-negative pathogens, namely *Acinetobacter*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* sensitive to a small number of drugs, if not any, are emerging as significant pathogens. The mechanisms of this resistance are often complex but include outer-membrane impermeability, up-regulated efflux pumps, target-site mutation and, not surprisingly, the production of carbapenemases, in addition to several enzymes. Given the frequency of worldwide reports now describing infection with carbapenemase-producing BGN, in addition to the intercontinental spread of hyper-epidemic clones, such as KPC-3-possesing *K. pneumoniae* ST258, it is possible that any institution on the globe could be beset by multi-resistant BGNs. Proficient methods are needed for early detection and confirmation in clinical microbiology laboratories of multidrug resistant bacteria, specially those producing carbapenemases, in any attempt aimed for targeting optimal antimicrobial therapy and controlling their spread. Therapeutic options for these pathogens are so extremely limited. Even now, resistance to new ''salvage'' therapy, such as tigecycline and colistin is being observed. Several new terms definitions have been introduced in the medical literature to describe this complex scenario: pan-resistance, extreme-resistance, extensively-resistant.

Although there is no international harmonization of this terminology, their adequately capture the public awareness for the desperate need for attention to this problem. As expected, mortality rates among patients with infections due to these organisms are significantly higher than those caused by sensitive germs. The urgency of the problem is compounded by the recognition that fewer new antimicrobial agents are introduced each year. Thus, clinicians are forced to use older drugs for which there is a lack of robust data about their effectiveness. The complex nature of this scenario requires the coordinated efforts of all sectors involved, in any attempt to curb antimicrobial resistance.

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61.002

Basic Principles of Implementing an Antibiotic Optimization Program

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Antimicrobial stewardship is an important and evolving aspect of patient care and safety programs in hospitals around the world. A team of involved specialists, including infectious diseases physicians, clinical microbiologists, hospital epidemiologists and others, is needed to address this complex problem. In United States a clinical pharmacist has been also claimed to collaborate in this kind of program, mentation. Two strategies, not to be exclusively applied, are proposed. Prospective audit with intervention and feedback is an option, while the use of formulary restriction and pre-authorization might be also used. The first strategy might be time consuming and requires a series of tools to succed. The implementation of the program requires administrative and economic support and the use of education, development of guidelines, antimicrobial order forms, de-escalation therapy (which requires an active participation of the microbiology laboratory), dose optimization, and switch to oral therapy. Effective use of antimicrobials but also prevention of resistance are the goals to achive in the individualised care of patients and new targets are being currently defined (pharmacodynamic objectives). Up to the moment more research is required to find the best ways to achieve these goals.

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61.003

Infection Control Program as an Additional Tool to Control Bacterial Resistance

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The combination of effective antimicrobial stewardship with a comprehensive infection control program has been shown to limit the emergence and transmission of antimicrobial-resistant bacteria, reducing health care costs.

There are multiple mechanisms postulated by which antimicrobial resistance may appear and disseminate within hospital organisms:

1) Introduction of a resistant organism to a previously susceptible population; 2) Acquisition of resistance by a susceptible strain: spontaneous mutation or genetic transfer; 3) Expression of regulated resistance already present in the population; 4) Selection of resistant subpopulations; and, 5) Dissemination or spread of resistant organisms

There have been proposed five strategic goals to optimize antimicrobial use: 1) Optimize antimicrobial prophylaxis for surgery 2) Optimize choice and duration of empirical therapy; 3) Improve prescribing by education; 4) Monitor and feedback information on antimicrobial resistance rates, and, 5) Produce protocols for antibiotic usage. Also the strategies must include optimal selection, dose, and duration of treatment, as well as control of antibiotic use, for prevention or slowing the emergence of resistant among microorganisms.

An effective Antimicrobial Control Program Infection must prevent or reduce antimicrobial resistance. Specific goals related to this program are:

1) A determination of who will be responsible for maintaining control. 2) A determination of which antimicrobial(s) to control. 3) Precise definitions of antimicrobial resistance for antimicrobials and organisms. 4) A system for monitoring the frequency of resistance (clinical and environmental). 4) Education. It is an essential element to influence prescribing behavior. 5) A method to determine antimicrobial use per geographic area per unit time. 6) Ability to distinguish community from nosocomial isolates. 7) A method to assure

that clinical care will not be harmed by control measures such as: de-escalation of therapy, dose optimization, and parenteral to oral conversion of antimicrobials with excellent bioavailability can decrease the length of hospital stay and health care costs.

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61.004

New Antibiotics: Which Role in a Antimicrobial Stewardship Program?

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Infections caused by multidrug-resistant bacteria continue to challenge physicians in the daily practice. We face growing resistance among Gram-positive and Gram-negative pathogens that cause infection in the hospital and in the community. Rice recently reported these as the ''ESKAPE'' pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) to emphasize that they currently cause the majority of world-wide hospital infections and effectively ''escape'' the effects of antibacterial drugs.

In this context, controlling antibiotic use and bacterial resistance trough an antibiotic stewardship program (ASP) is of major importance to all professionals involved in infectious diseases.

A critical need to develop new antimicrobial compounds and to use the recently approved agents appropriately are components of all ASP. Unfortunately, most of the agents which are in the late stage of develop have activity only against Gram-positives and none is active for treatment of infections caused by the Gram-negative ESKAPE pathogens.

We have analized the body of the literature with the aim to define, within a ASP, the opportunity of use and the potential advantages of new antibiotics in order to reduce the emergence and selection of resistant pathogens.

Related with the role of the new antibiotics in a Asp, it is possible to consider the following points: i-the use of tigecycline instead of carbapenems in clinical settings with high rates of carbapenems-resistant pathogens (ie. in nosocomial peritonitis), ii-the use of doripenem in extended-infusion (ie. in severe infections due to *Pseudomonas aeruginosa*); iii-the use of daptomycin at high doses (ie. in infections due to methicillin-resistant *Staphylococcus aureus*) and iv-the use of ceftobiprole as empiric monotherapy (ie. in some suspected mixed infections).

The use of the new antibiotics in the daily practice based on the individual patient characteristics, causative organism, site of infection, and pharmacokinetic and pharmacodynamic characteristics of the drug is an important part of an ASP.

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Current challenges in HIV care (Invited Presentation)

62.001

State of the Art on ARV Therapy: How Many Standards of Care?

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Albeit nobody would support the idea of ''first and second class medicine'', in real life we confront AIDS with at leat two standards of care. When to start ARV therapy remains a matter of debate. No disagreement exists for symptomatic patients, as well as for asymptomatic individuals with CD4 counts of 350/ mm3 or below. In resource-poor settings, WHO recommended until late 2009 that adolescents and adults should start HAART when they have advanced HIV disease, mildly symptomatic and asymptomatic disease, WHO Stage II or I HIV disease with CD4 counts <200/mm3 .These recommendations were updated in November 2009 and look now closer to those released by other international bodies. Some Western countries guidelines panels, like the DHHS recommends now treatment initiation in asymptomatic patients when the CD4 count falls below 350/mm3, and have shown a divided opinion regarding the if treatment should be considered in patients with CD4 cell counts <500/mm3, particularly if the patient has high viral load, age above 50 and/or comorbidities like HBV or HCV coinfections, among others. Increasing amount of data suggest that by starting earlier, the so called ''non-AIDS'' diseases driving to mortality in the HAART era might be dramatically reduced. On top of the benefits at the individual level, ART has been shown as a prevention tool by reducing the median viral load at the community level.Currently available co formulations are the best options for ARV backbone in naive patients. Issues such as childbearing potential and baseline resistance need to be taken into consideration when selecting a regimen. Controversies remain on whether to use a PI or an NNRTI as the third drug in initial therapy, particularly important in the presence of advanced disease. The bottom line is that one size does not fit for all in this challenging field.

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62.002

Drug Resistance and Other Laboratory Monitoring Assays in HIV infection

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Although CD4 cell counts and plasma viral load assays are the principal laboratory tests used to monitor the progress of HIV-1 infections, several other assays are assuming increasing importance to adequately assess the benefits of antiretroviral therapy (ART) in infected individuals. The accessibility of such assays will vary greatly, depending on the resources available to treat HIV infections.

Where testing capability exists, HIV drug resistance testing is useful when patients enter care prior to initiating therapy and again when considering change of regimens